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SPECIAL ARTICLE

New Insulin Delivery Recommendations

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Abstract

Many primary care professionals manage injection or infusion therapies in patients with diabetes. Few published guidelines have been available to help such professionals and their patients manage these therapies. Herein, we present new, practical, and comprehensive recommendations for diabetes injections and infusions. These recommendations were informed by a large international survey of current practice and were written and vetted by 183 diabetes experts from 54 countries at the Forum for Injection Technique and Therapy: Expert Recommendations (FITTER) workshop held in Rome, Italy, in 2015. Recommendations are organized around the themes of anatomy, physiology, pathology, psychology, and technology. Key among the recommendations are that the shortest needles (currently the 4-mm pen and 6-mm syringe needles) are safe, effective, and less painful and should be the first-line choice in all patient categories; intramuscular injections should be avoided, especially with long-acting insulins, because severe hypoglycemia may result; lipohypertrophy is a frequent complication of therapy that distorts insulin absorption, and, therefore, injections and infusions should not be given into these lesions and correct site rotation will help prevent them; effective long-term therapy with insulin is critically dependent on addressing psychological hurdles upstream, even before insulin has been started; inappropriate disposal of used sharps poses a risk of infection with blood-borne pathogens; and mitigation is possible with proper training, effective disposal strategies, and the use of safety devices. Adherence to these new recommendations should lead to more effective therapies, improved outcomes, and lower costs for patients with diabetes.

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Correct technique in insulin delivery is critical for optimal control of diabetes. This article reviews the most recent studies in the field and then offers new injection and infusion recommendations for insulin users. It is meant to complement and extend the injection recommendations published in 2010.[1] These latest recommendations were based on the results of the fourth Injection Technique Questionnaire (ITQ) survey (published elsewhere in this issue). From February 2014 through June 2015, 13,289 insulin-injecting patients with diabetes from 42 countries participated in the ITQ survey, one of the largest multinational studies of its kind. A smaller Infusion Technique Questionnaire survey was undertaken concurrently with the ITQ in 356 patients using continuous subcutaneous insulin infusion (CSII) in four countries and informed the drafting of the new infusion recommendations.

The ITQ survey results (for injection and infusion) and the initial draft of these recommendations were presented at the Forum for Injection Technique and Therapy: Expert Recommendations (FITTER) workshop held in Rome, Italy, on October 23 and 24, 2015, at which 183 physicians, nurses, educators, and allied health care professionals (HCPs) from 54 countries (see the list in Supplemental Appendix 1, available online at http://www.mayoclinicproceedings.org)[2] met to debate, revise, and adapt these proposals. FITTER was the fourth in a series of expert workshops that have issued recommendations on insulin delivery.[1,3-5]

MATERIALS AND METHODS

Publications were identified using Medline, EMBASE, PubMed, and Cochrane Controlled Trials. The search was focused on the period between January 2008 and December 2015,

For editorial comment, see page 1155; for related articles, see pages 1212 and 1224

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although we had at our disposal the medical literature going back to 1980. We used the terms *subcutaneous injections*, *insulin*, *injection technique, insulin infusion, CSII sets, infusion sets,* and *glucagon-like peptide-1 receptor agonists* (GLP-1). For those seeking other related terms, a glossary is also available as Supplemental Appendix 2 (available online at http://www.mayoclinicproceedings.org).[2] Of 368 articles found, 254 met the criteria for inclusion as outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[6]

One of us (K.W.S.) drafted the initial version of the recommendations. This draft was then extensively revised during 12 monthly web conferences with a group of international experts in injection and infusion techniques (see authors). This new draft was then extensively revised by the 183 expert invitees to the FITTER meeting in Rome. After FITTER, additional revisions were made by FITTER attendees. The current version reflects the collective input of these diabetes experts from around the world and bears little resemblance to the earlier drafts.

The panel used a previously established scale[1,4,7] for the strength of each recommendation: A = strongly recommended, B = recommended, and C = unresolved issue. For grading the degree of scientific support for each recommendation, we used the following scale: 1 = at least 1 rigorously performed study that is peer reviewed and published (excludes observational studies); 2 = at least 1 observational, epidemiologic, or population-based published study; and 3 = expert consensus opinion informed by broad patient experience.

This simplified version of the grading scales commonly used[7] was believed to be more appropriate for our field, where randomized, controlled outcome trials are rarely available but good-quality studies on the performance of devices do exist. Each recommendation is followed by a letter and number in bold (eg, **A2**). The letter indicates the importance that the recommendation should have in practice, and the number indicates its level of evidence in the medical literature. The most relevant publications bearing on a recommendation are also cited or summarized. Although these recommendations will be suitable for most patients, individual exceptions may occur for which the guidelines should be adapted.

ANATOMY

Skin Thickness

The skin is the first obstacle a needle must traverse when giving an injection or infusion. A variety of studies of adult skin at injection sites using various imaging techniques have all shown similar results: the skin varies in thickness from approximately 1.25 to 3.25 mm in 90% of individuals and averages approximately 2.0 to 2.5 mm. Studies have included both healthy volunteers and persons with diabetes, and their results are consistent across age groups, sexes, body mass indexes (BMIs), and geographic locations. Studies included four ethnic groups in the United States[8]; Italian[9] and South African[10] children and adolescents with type 1 diabetes; and groups of Chinese,[11] Indian,[12] Filipino,[13] and Korean adults[14] (most with type 2 diabetes). Details of these studies are summarized in Supplemental Figure 1[8] and Supplemental Tables 1-4 (available online at http://www.mayoclinicproceedings.org).[9-15]

The skin is slightly less thick in children, but by puberty it increases to adult levels. However, these differences are small and are irrelevant for insulin injections and infusions. In both children and adults, even the shortest needles (4 mm) reliably traverse the skin and enter the subcutaneous (SC) fat.

SC Thickness

The distance from the surface of the skin to the muscle fascia (ie, the sum of skin and SC thickness) determines the potential for intramuscular (IM) injection. Compared with skin thickness, which is relatively constant, SC tissue thickness varies widely. Ultrasound measurements of skin and SC thickness at insulin injection sites in adult patients with diabetes have recently been published.[11,13] See Supplemental Tables 1-4[9-15] for a summary of findings from the most important of these studies. Gibney et al[8] and Hirsch et al[15] (separate reports on the same study) measured SC fat depth at single locations in the thigh, arm, abdomen, and buttock. Studies by Ludescher et al[16] and Sim et al[14] (where 8-10 measurements were taken and averaged for each body site) largely confirmed the ultrasound study findings from a single site.

Several rules of thumb have emerged from these studies: SC fat thickness increases in

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direct proportion to BMI; women, on average, have an approximately 5-mm greater SC fat thickness than men at the same BMI; and truncal sites (abdomen and buttocks) have thicker SC fat layers than limbs (thighs and arms) in the same individual. The most important outcome of these studies is that they inform us about the risk of IM injections. Intramuscular deposition of insulin leads to unpredictable (largely faster) absorption of insulin and destabilization of the blood glucose level. Intramuscular injections occur more frequently with longer needles, in slimmer and younger patients, males, and in those who use limbs rather than truncal sites for insulin delivery.

Supplemental Tables 5-9[8,11,14,15] (available online at http://www.mayoclinicproceedings.org) provide estimates of the IM injection risk by site, needle length, and patient type. Different risk estimates in several studies reflect differing patient populations with a wide range of average BMIs.

Children aged 0 to 2 years have higher BMIs and more SC tissue than preschool children. Preschool children (2-6 years old) are usually at the thinnest point in their lives, and both sexes usually have very little SC tissue. School-age children (7-13 years old) slowly gain SC tissue, but there are few sex differences until puberty. During puberty, young women gain considerably more SC tissue than young men owing to hormonal influences. See Supplemental Tables 1-4[9-15] for a summary of findings from the most important pediatric studies. See Supplemental Table 10[9,10] (available online at http://www.mayoclinicproceedings.org) for estimates of IM risk in pediatric patients by site, needle length, and patient age.

PHYSIOLOGY

Risk of IM Injections

Insulin absorption rates from IM injections differ according to the activity of the muscle. Muscle can be resting (eg, abdominal muscles in a recumbent person), active (abdominal muscles in a standing person), or exercising (abdominal muscles in a person doing sit-ups). Intramuscular-injected insulin is absorbed differently in resting, active, and exercising muscle, with the rate increasing as one progresses through the 3 stages.

Human insulins and analogues have different absorption profiles when deposited into muscle. Intramuscular injections, especially into working muscle, can distort absorption and, thus, decouple maximum blood glucose levels from peak insulin activity. This can cause poor glycemic control, including excessive glycemic variability. Intramuscular injections can lead to frequent and unexplained hypoglycemia according to several studies.[17-19]

Patients may be unaware that they are injecting IM. Several clinical pointers can give clues as to whether the injection is IM or SC. Intramuscular injections can lead to a greater risk of bleeding, bruising, and pain. The pain may be described as stinging, and it worsens if the relevant muscle is contracted with the needle in situ. If a patient releases the syringe with the needle still under the skin, it may continue to stand upright if it is IM (whereas it topples over in SC injections).[20] Unexplained glycemic variability and episodes of hypoglycemia may suggest IM injection. At special risk are children, thin persons, and persons using longer needles or following improper technique.

Needle Length

The needle lengths that were once recommended for SC injection (for adults, $\geq$8 mm; for children, $\geq$6 mm) are now known to be too long because they increase the risk of IM injections without evidence of improved glucose control.[21-23] Shorter needles are much safer and are better tolerated and less painful. Hirsch et al[24] compared a 4-mm pen needle with 5- and 8-mm needles in a large randomized controlled study. The 4-mm needle was shown to be safe and efficacious in adult patients of all sizes (ie, equivalent glucose control); skin leakage was equivalent and pain scores were improved with the 4-mm needle. Similar studies have been performed in various other groups,[25-27] including obese patients.[28] All earlier studies on needle length[29-37] have also shown similar glucose control (glycated hemoglobin, glycated albumin, or fructosamine) without increased leakage with the shorter-length needle. The shortest-length pen needle is 4 mm, but the shortest syringe needle today is 6 mm long (the syringe needle has to pass through the vial septum or stopper). Insulin pharmacokinetics/pharmacodynamics has been shown to be the same when injected into resting individuals using short and long needles.[27,38,39] A summary of these needle

length and insulin absorption studies is presented in Supplemental Appendix 3 (available online at http://www.mayoclinicproceedings.org).[32,36,40-70]

Recommendations.

- The 4-mm needle is long enough to traverse the skin and enter the SC tissue, with little risk of IM (or intradermal) injection. Therefore, it is considered the safest pen needle for adults and children regardless of age, sex, ethnicity, or BMI. **A1**
- The 4-mm needle may be used safely and effectively in all obese patients. Although it is the needle of choice for these patients, a 5-mm needle may also be acceptable. **A1**
- The 4-mm needle should be inserted perpendicular to the skin (at 90° to the skin surface), not at an angle, regardless of whether a skinfold is raised. **A1**
- Very young children (≤6 years old) and very thin adults should use the 4-mm needle by lifting a skinfold and inserting the needle perpendicularly into it. Others may inject using the 4-mm needle without lifting a skinfold. **A1**
- The safest currently available syringe needle for all patients is 6 mm in length. However, when any syringe needle is used in children (≥6 years old), adolescents, or slim to normal-weight adults (BMI of 19-25 [calculated as the weight in kilograms divided by the height in meters squared]), injections should always be given into a lifted skinfold. **A1**
- Use of syringe needles in very young children (<6 years old) and extremely thin adults (BMI <19) is not recommended, even if they use a raised skinfold, because of the excessively high risk of IM injections. **A1**
- Health care authorities and payers should be alerted to the risks associated with using syringe or pen needles 6 mm or longer in children. **A2**
- Children still using the 5-mm pen needle should inject using a lifted skinfold. Children using pen needles 5 mm or longer should be switched to 4-mm pen needles if possible and if not should always use a lifted skinfold. **A2**
- Injecting at a 45° angle using a 6-mm needle is an acceptable substitute for lifting a skinfold because the net penetration of a 45° injection using the 6-mm needle is approximately 4 mm.[71] **A1**
- If arms are used for injections with needles 6 mm or longer, a skinfold must be lifted. This requires that the injection be given by a third party. **A2**
- Avoid pushing the needle hub in so deeply that it indents the skin because this increases the risk of IM injections. **B3**
- Patients with tremors or other disorders that make them unable to hold a 4-mm pen needle in place may need longer needles. **B3**
- High-flow needles (with extra-thin walls) have been shown to be appropriate for all injecting patients. Their obstruction, bending, and breakage rates are the same as for conventional-quality needles (extremely low) and offer flow and ease-of-use advantages. **A3**

Site Care

The recommended injection and infusion sites are the abdomen, thigh, buttock, and upper arm.[72-76] Suggested boundaries in these sites for insulin delivery are stated in the golden rules (see the Appendix).

Recommendations.

- Patients should inspect the site before injection. Injections should be given into clean sites, only using clean hands.[77-79] **A2**
- If the site is found to be unclean it should be disinfected. Disinfection is also required in institutional settings such as hospitals and nursing homes. If alcohol is used, it must be allowed to dry completely before the injection is given.[80,81] **A2**
- Disinfection is usually not required when injections are given in noninstitutional settings such as homes, restaurants, and workplaces.[82-86] **A3**
- Patients should never inject into sites of lipohypertrophy (LH), inflammation, edema, ulceration, or infection.[84-92] **A1**
- Patients should not inject through clothing because they cannot inspect the site beforehand or easily lift a skinfold.[80] **B2**

Proper Use of Pens

When patients use pens they usually cannot see the insulin going in as they can with a syringe. Obstruction of insulin flow with

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pens, although rare, can have serious consequences. When teaching patients proper pen use, HCPs should consult the instruction manual for the specific device being used.

Several basic steps are important to follow with any pen injector, but few of these are known by (or taught to) patients. For example, it is important not to accidentally push the thumb button before the pen needle tip is inserted in the SC tissue. In fact, it is best not to touch the thumb button until the needle is completely inserted. Once the thumb button is pushed, patients should keep pressure on it until the needle is completely withdrawn from the body. If the button is released while the needle is still in the skin, body fluid and cells may be aspirated into the cartridge and contaminate it.[93] Another important step is to always push the button vertically (along the axis of the pen). Some patients, especially the frail or elderly, are unable to completely inject their total dose because they are pushing the button obliquely, eg, by pushing on its edge, generating excessive resistance along its glide path.[94,95]

Recommendations.

- Pens should be primed before injections to ensure free and unobstructed flow. Manufacturer's instructions should be followed. Priming entails seeing at least a drop of insulin at the tip of the needle. Once free flow is verified, the patient may dial the desired dose and inject.[96,97] **A3**
- Pens and their cartridges are for single-person use only and should never be shared among patients. Otherwise, biologic material from one person can be drawn into the cartridge and then injected into another person.[82,98] **A2**
- After use, needles should not be left attached to the pen but rather disposed of immediately. Otherwise, air or other contaminants can enter the cartridge or medication can leak out, both of which can distort dose accuracy.[45,99-103] **A2**
- Pen needles should be used only once. They are no longer sterile after use.[3,4,83,84,88,103-105] **A2**
- The thumb button should be touched only after the pen needle is fully inserted. After that, the button should be pressed along the axis of the pen, not at an angle.[99] **A2**
- After the thumb button is completely pushed in, patients should count slowly to 10 and then withdraw the needle from the skin. This is necessary to prevent medication leakage and to get the full dose.[45,105-108] **A1**
- Some patients may need to count past 10, especially when giving higher doses. Counting only to 5 may be acceptable for lower doses. Patients may find the right time for themselves by trial and error, using leakage or dribbling of insulin as a guide. **A3**
- Pressure should be maintained on the thumb button until the needle is withdrawn from the skin to prevent aspiration of patient tissue into the cartridge.[100,101] **A2**

Proper Use of Syringes

Although insulin pens continue to grow in popularity, there are still many regions of the world where syringes are used extensively. Each syringe has scale markings appropriate for only one concentration of insulin, and mismatches of syringes to insulin can lead to serious underdosing or overdosing. In some countries, both U-40 and U-100 insulin may be on the market together. In others, concentrations varying from U-100 to U-500 may be simultaneously available. Patients should avoid using syringes with detachable needles because permanently attached needle syringes deliver better dose accuracy, have far less dead space, and allow the mixing of insulins if needed. Currently, there are no syringes with needles less than 6 mm in length because of incompatibility with some vial stoppers.[109]

Recommendations.

- Syringe users should ensure that their device is appropriate for the concentration of insulin they are using. **A3**
- When drawing up insulin from a vial, the user should first draw air into the syringe at a dose equal to (or slightly greater than) the dose of insulin to be given. This air is then injected into the vial to facilitate withdrawal of insulin. **A3**
- If air bubbles are found in the syringe, tap on the barrel to bring them to the surface. They may then be removed by pushing the plunger up. **A3**
- With syringes, unlike pens, the needle does not need to be left under the skin for a count

of 10 after the plunger has been fully depressed.[105,106,110] **A3**
- Syringe needles should be used only once. They are no longer sterile after use.[3,4,83,84,88,109,111,112] **A2**

Insulin Analogues and Other Injectables (GLP-1 Receptor Agonists)

Few studies address proper injection technique with these newer agents. Earlier studies suggested that absorption rates of rapid-acting analogues are similar between fat tissue and resting muscle; absorption from working muscle was not tested.[111,112]

Recommendations.

- Rapid-acting analogues can be given at any of the injection sites. Rates of absorption have not been shown to be site specific.[113-115] **A2**
- Intramuscluar injection of rapid-acting insulin analogues should be avoided if possible.[116] **A2**
- Similarly, long-acting analogues may also be given at any of the injection sites. However, IM injection should be scrupulously avoided because it can lead to profound hypoglycemia.[115,117] **B2**
- Pending further studies, patients using non-insulin injectable therapies (such as GLP-1 receptor agonists) should follow the established recommendations for insulin injections (regarding needle length, site selection, and rotation).[107,116] **A2**

Human Insulins

Regular insulin (also known as soluble human insulin) has a slower absorption rate than rapid-acting analogues. Neutral protamine Hagedorn (NPH) insulin and other older long-acting insulins have absorption peaks that can lead to hypoglycemia, especially when given in larger doses.

Recommendations.

- It is preferable that NPH (when given alone) be injected at bedtime rather than earlier in the evening to reduce the risk of nocturnal hypoglycemia. **A1**
- Intramuscular injections of NPH and other long-acting insulins must be strictly avoided because of the risk of serious hypoglycemia (Anders H. Frid, MD, oral communication, October 24, 2015).[17,117] **A2**
- The preferred site for regular (soluble human) insulin is the abdomen because absorption of this insulin is fastest there.[21,38,118-120] **A1**
- The regular/NPH insulin mix should be given in the abdomen to increase the speed of absorption of the short-acting insulin to cover postprandial glycemic excursions.[18] **A1**
- If there is a risk of nocturnal hypoglycemia, NPH and NPH-containing insulin mixes given in the evening should be injected into the buttock or thigh because these sites have slower absorption rates for NPH insulin.[79,121,122] **A1**

Lifting a Skinfold

Lifting a skinfold is required when the distance from the skin surface to the muscle is less than or equal to the needle length. Lifting a skinfold in the abdomen nearly doubles the skin-to-muscle distance. In the thigh, it is sometimes difficult to lift a skinfold, and the mean increase in skin-to-muscle distance may be only 20%. In thin patients, thigh skinfolds may actually decrease the distance to muscle fascia—the exact opposite of what is desired.[42] Lifting a skinfold is rarely needed in the buttocks because of the abundance of SC tissue there. When performed in the arm, skinfolds must be lifted by someone other than the patient.

Recommendations.

- A correct fold is made by lifting the skin with the thumb and index finger (possibly adding the middle finger). If the skin is lifted using the whole hand, muscle may be lifted as well as SC tissue, which can lead to IM injections.[123] **A3**
- Skinfolds should be lifted gently and not squeezed so tightly as to cause blanching or pain. **A3**
- The optimal sequence when injecting into a skinfold is as follows: (1) gently lift a skinfold, (2) inject the insulin slowly at a 90° angle to the surface of the skinfold, (3) let the needle remain in the skin for a count of 10 after the plunger is depressed (when using a pen), (4) withdraw the needle from

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the skin at the same angle it was inserted, (5) release the skinfold, and (6) dispose of the used needle safely. **A3**

Cloudy Insulin Resuspension

Several studies have shown that cloudy insulins are often inadequately resuspended.[110,124-127] Crystals of insulin must be mechanically agitated so that they go back into solution before injection, but many patients do not know how to do this or do it inappropriately. Inadequate resuspension can lead to varying concentrations of insulin and unpredictable clinical responses. A summary of key studies on insulin resuspension can be found in Supplemental Appendix 4 (available online at http://www.mayoclinicproceedings.org).[124-129]

Recommendations.

- Gently roll and tip cloudy insulins (eg, NPH and premixed insulins) until the crystals are resuspended (the solution becomes milk white).[110,124-129] **A2**
- Tipping involves one full up-down motion of the pen or vial, and rolling is a full rotation cycle between the palms. One evidence-based method involves rolling the insulin cartridge horizontally between the palms 10 times for 5 seconds, then tipping 10 times for 10 seconds at room temperature.[129] **A2**
- Visually confirm that the resuspended insulin is sufficiently mixed after each rolling and tipping, and repeat the procedure if crystal mass remains in the cartridge. **A2**
- Vigorous shaking should be avoided because this produces bubbles that will affect accurate dosing. Avoid exposing insulin to direct heat, light, or excessive agitation. **A2**
- Store unopened insulin in a refrigerator in which there is no risk of freezing. **A2**
- After initial use (in pen, cartridge, or vial), insulin should be stored at ambient temperature (15°-30°C or 59°-86°F) for up to 30 days or according to the manufacturer's recommendations and within expiration dates. Premixed insulin pens and some of the newer insulins may vary in storage guidelines, so patients should check the manufacturer's recommendations.[129-131] **A2**
- If room temperatures exceed 30°C (86°F), then insulin in current use should be stored in a refrigerator. It should be allowed to warm up before injection. Insulin can be warmed by rolling it between the palms. **A2**

Pregnancy

Studies are still lacking on the optimal injecting technique during pregnancy, but the following recommendations are considered reasonable.

Recommendations.

- When fetal ultrasound is performed, SC fat patterns in the mother may be assessed at the same time and recommendations given to her regarding safe zones for injections.[132] **B2**
- The abdomen is generally a safe site for insulin administration during pregnancy. Given the thinning of abdominal fat from uterine expansion, pregnant women with diabetes (of any type) should use a 4-mm pen needle. **B2**
- *First trimester*: Women should be reassured that no change in insulin site or technique is needed. **B2**
- *Second trimester*: Insulin can be injected over the entire abdomen as long as properly raised skinfolds are used. Lateral aspects of the abdomen can be used to inject insulin when no skinfold is raised. **B2**
- *Third trimester*: Injections can be given into the lateral abdomen as long as they are made into properly raised skinfolds. Apprehensive patients may use the thigh, upper arm, or buttock instead of the abdomen. **B2**

Role of the HCP

Currently there are 3 classes of injectable therapies for diabetes: insulin, GLP-1 receptor agonists, and amylin analogues.[41,133,134] Of these, only insulin is in common use for CSII. Despite more than 90 years of use, insulin injections and infusions are often performed incorrectly, with adverse clinical consequences for patients and additional costs for payers. Often, even simple rules are not taught or followed. The HCP has a crucial role in the proper use of these therapies. Proper technique is essential to achieve optimal diabetes control, reduce variability,

and achieve desired outcomes.[18,85,119,135-138] Often the most important determinant of patients' injection technique is the knowledge and commitment of their HCP.

Recommendations.

- Key tasks of the HCP include helping patients (and caregivers) overcome the psychological obstacles related to injecting or infusing, especially at the initiation of treatment, and then teaching them how to perform the procedure correctly. **A2**
- The HCP must understand the anatomy and physiology of insulin delivery sites so that IM injections/infusions, LH, leakage, and other complications are avoided. **A2**
- The HCP must understand the pharmacokinetics of the therapeutic agents and the absorption profiles of the various delivery sites. **A2**

Therapeutic Education

Decisions regarding insulin therapy should be made jointly by the HCP and the patient (and caregivers).[137,138] Not all patients receive appropriate education about injections/infusions, and not all essential topics are covered.[139-141] Education in a group setting may lead to better adherence and lower glycated hemoglobin values if the HCP has training as an educator.[142] A summary of studies on therapeutic education for insulin delivery can be found in Supplemental Appendix 5 (available online at http://www.mayoclinicproceedings.org).[143,144]

Recommendations.

- Explore anxieties about insulin and the injecting/infusing process.[139,145] **A3**
- Discuss each of the essential topics (see the next recommendation) at initiation of therapy and at least once a year thereafter. Make sure that information is delivered verbally and in writing and has been fully understood.[146] **A3**
- Essential topics include the injecting/infusing regimen; the choice and management of the devices used; the choice, care, and self-examination of injection sites; proper injection techniques (timing, site rotation, injection angle, skinfolds, insulin storage, resuspension of cloudy insulin, etc); injection complications and how to avoid them; optimal needle lengths; safe disposal of used sharps; and psychological hurdles and aids to overcome them.[137-139,143,146-149] **A1**
- Instructions should be given in verbal and written form, and adherence should be checked. To confirm adherence to prescriptions, ask to see the needles, insulin, and other devices from the latest batch received from the pharmacy. **A3**
- Assess each injection/infusion site visually and by palpation, if possible, at each visit but at minimum once a year.[139,143,150] **A3**

PATHOLOGY

Lipohypertrophy

Lipodystrophy is a disorder of fat tissue. There are 2 main types of lipodystrophy: lipoatrophy, which is loss of adipocytes that clinically manifests as indenting and cratering, and LH, which is enlargement of adipocytes that manifests as swelling or induration of fat tissue.[151] An even rarer type of lipodystrophy is amyloidosis,[152-155] for which a biopsy and pathologic diagnosis are usually necessary. Insulin injected into amyloid deposits may have substantially impaired absorption. Usually, LH regresses after stopping insulin injections into the lesions, whereas localized amyloidosis does not. Distinguishing these lesions is clinically important.

Lipohypertrophy is common, although studies vary on the exact frequency. A Spanish study[156] found LH in nearly two-thirds of injecting patients (64.4%) (type 1 diabetes, 72.3% vs type 2 diabetes, 53.4%). An Italian study[143] found the prevalence to be 48.7%, and in a Chinese study[157] it was 53.1%. The absorption of insulin injected into LH lesions may be erratic and unpredictable, which can lead to hyperglycemia, unexpected hypoglycemia, or increased glucose variability.[158,159] Conversely, patients who switch from injecting into LH lesions to normal tissue are at risk for hypoglycemia unless they lower their doses. A summary of additional studies in LH and pointers for optimizing the physical examination for LH are presented in Supplemental Appendix 6 (available online at http://www.mayoclinicproceedings.org) (Irl B. Hirsch, MD, oral communication, October 24, 2015).[88,160-177] Lipoatrophy studies are also summarized at this site.

Recommendations.

- Sites should be examined by the HCP for LH at least once a year, or more frequently if LH is already present. It is often easier to palpate LH than to see it. Use of a lubricating gel facilitates palpation.[139,178] **A2**
- The physical examination for LH is ideally performed with the patient lying down and disrobed to the underwear. But in circumstances that preclude this, examination of the patient sitting, standing, or partially clothed is acceptable. **A3**
- Teach patients to inspect their own sites, and give training in site rotation, proper injection technique, and detection and prevention of LH. **A2**
- After obtaining patient consent, make 2 ink marks at the extreme edges of LH with a single-use skin-safe marker. This will allow the LH to be measured for future assessment. If visible, the lesions could also be photographed. **A2**
- Patients should be encouraged to avoid injecting into areas of LH until the next examination by an HCP. Use of larger injection zones, correct injection site rotation, and non-reuse of needles should be recommended.[179,180] **A2**
- Switching injections away from LH and to normal tissue often requires a decrease in the dose of insulin injected. The amount of decrease varies from one individual to another and should be guided by blood glucose measurements. Reductions often exceed 20% of their original dose.[87] **A1**

Rotation of Injection Sites

A variety of studies have shown that the best way to safeguard normal tissue is to consistently and properly rotate injection sites.[181,182] Injection can be rotated from one body region to another (abdomen to thigh, to buttock, to arm), but note that absorption characteristics change depending on the type of insulin given. Analogues may be given at any injection site with similar uptake and action (pharmacokinetics/pharmacodynamics), but human insulins (regular, NPH) vary substantially, with absorption being fastest from the abdomen and slowest from the buttocks. Correct rotation involves spacing injections a least 1 cm (approximately the width of an adult finger) apart even within an injection zone. Additional study summaries on rotation are presented in Supplemental Appendix 7 (available online at http://www.mayoclinicproceedings.org).[2]

Recommendations.

- Injections should be systematically rotated to avoid LH. This means injecting at least 1 cm (or approximately the width of an adult finger) from previous injections, a vital procedure that requires careful planning and attention. **A2**
- Patients should be given an easy-to-follow rotation scheme from the beginning of injection/infusion therapy. The HCP should review the site rotation scheme with the patient at least once a year.[182-188] **A2**
- One evidence-based scheme involves dividing injection sites into quadrants (or halves when using the thighs or buttocks), using one quadrant per week, and rotating quadrant to quadrant in a consistent direction (eg, clockwise) (scheme courtesy of Lourdes Saez-de Ibarra and Ruth Gaspar, diabetes nurses and specialist educators at La Paz Hospital, Madrid, Spain). **A3**

Needle Reuse

Many insulin injectors find it burdensome to carry extra needles when away from home. They also are reluctant to carry containers to dispose of used needles. Sometimes patients have to pay a portion or the entire cost of their needles, and some decide that it is not worth it to buy a new needle for each injection. Others find that the injections from reused needles are not noticeably more painful, as long as they do not reuse excessively. Finally, some patients believe that disposing of a needle after 1 use is ecologically wasteful because the metal and plastic must be incinerated.

However, official labeling on needles requires both single-use and sterility symbols. Labeling is linked to responsibility so that when HCPs advise against the official labeling they assume the responsibility for adverse outcomes. Published injection technique recommendations have usually opposed needle reuse,[83,92,189] for the reasons reviewed in studies summarized in Supplemental Appendix 8 (available online at http://www.mayoclinicproceedings.org),[190-193] but they

stop short of declaring it seriously harmful to the patient.

It seems that needle reuse, particularly reuse frequency, is associated with the development of LH. Local skin or SC tissue infections, injection pain, and unpleasantness have not been clearly associated with limited needle reuse (until needle blunting occurs). The lack of infectious complications may be attributed to the antimicrobial preservatives in insulin preparations.

Recommendations.

- There is an association between needle reuse and LH, although a causal relationship has not been proved. There is also an association between reuse and injection pain or bleeding. Patients should be made aware of these associations. **A2**
- Reusing insulin needles is not an optimal injection practice, and patients should be discouraged from doing so. Elsewhere in these recommendations it is stated that pen needles (and syringe needles) should be used only once. They are no longer sterile after use.[3,4,83,84,88,109-111] **A2**
- However, patients who reuse needles should not be subjected to alarming claims of excessive morbidity from this practice. **A3**

Bleeding and Bruising

Needles will occasionally hit a blood vessel or a capillary bed, producing local bruising or bleeding.[194] Today's needles are of much smaller diameter than they once were, and the amount of blood loss is usually inconsequential. Applying pressure to the site for 5 to 10 seconds should stop the bleeding. Varying the needle length does not alter the frequency of bleeding or bruising.

Recommendations.

- Patients should be reassured that local bruising and bleeding do not adversely affect clinical outcomes or the absorption of insulin. **A2**
- If bleeding and bruising are frequent or excessive, the injection technique should be carefully assessed as well as the presence of a coagulopathy or the use of anticoagulant or antiplatelet agents. **A3**

Leakage of Insulin

There are 3 types of leakage. Leaking from the pen is due to a poor seal between the needle and the cartridge in the pen. Dripping from the needle (while it is on the pen) can occur when the plunger is not held down correctly or the needle is taken out of the skin too soon. Reflux or backflow out of the injection site can happen when the needle is taken out too soon or for some other reason (obese patient). Additional studies on leakage are summarized in Supplemental Appendix 9 (available online at http://www.mayoclinicproceedings.org).[195,196] Data on innovations in needle geometry are available in Supplemental Appendix 10 (available online at http://www.mayoclinicproceedings.org).[197-199]

Recommendations: Leakage at Cartridge and Pen Needle Connection.

- Ensure that the pen needle is ISO-certified compatible with the insulin pen. **A3**
- Position the pen needle along the axis of the pen before screwing or snapping it on. **A3**
- Pierce straight through the septum of the cartridge. **A3**

Recommendations: Dripping From the Needle.

- Use needles that have a wider inner diameter and improved insulin flow (eg, extra-thin-walled needles).[200,201] **A1**
- Count to 10 after the plunger is fully depressed before removing the needle from the skin to allow time for expulsive forces to be transmitted through all pen parts to the insulin column in the cartridge. **A2**
- By trial and error, patients may learn how long they need to hold the button down and the needle under the skin to avoid dripping from the needle tip or backflow out of the skin. This may be less than 10 seconds. **A2**
- Larger doses may be split to reduce the volume of insulin. **A2**

Recommendations: Skin Leakage.

- Use needles with thin-wall or extra-thin-wall technology. **A1**
- Count to 10 after the plunger is fully depressed before removing the needle from the skin. This allows enough time for the injected medication to spread out through

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the tissue planes and to cause the tissue to expand and stretch. **A2**

- A small amount of skin leakage (a little pearl of liquid at the injection site) can be ignored. It is almost always clinically insignificant. **A1**
- For patients who report frequent skin leakage, direct observation of their self-injection is important for detecting possible technique-related issues that can be modified. **A2**

PSYCHOLOGY

Beginning insulin therapy can be fraught with psychological hurdles, regardless of the age of the patient. Foremost among these is the fear of pain. Insulin injections are usually not painful, except in the event that the needle hits a nerve ending, which is quite infrequent. Nevertheless, some patients are quite sensitive to sensations described as painful. Patient awareness of injection discomfort has been studied extensively and is related to 3 key factors: needle length, needle diameter, and injection context. Injection context includes the environment (eg, noise and the presence of other people), the appearance of the needle, and the anxieties of the HCP and the family. The more apprehension the latter display, the greater the pain and anxiety felt by the patient.[202,203] This reverse transference places a large responsibility on caregivers to assess their own attitudes toward injection pain. Some patients note discomfort when injecting insulins that have a low pH. This seems, anecdotally, to be reported more commonly in children. Other studies on the psychology of insulin delivery are summarized in Supplemental Appendix 11 (available online at http://www.mayoclinicproceedings.org).[204-225]

Recommendations

Emotional and Psychosocial Issues.

- Show empathy by addressing the patients' emotional concerns first. The HCP should explore worries and barriers to treatment and acknowledge that anxiety is normal when beginning any new medication, especially injection therapy. **A2**
- All patients, but especially adolescents, should be encouraged to express their feelings about injecting/infusing, particularly their anger, frustration, or other struggles. **A3**
- Patients of all ages should be reassured that this is a learning process and that the health care team is there to help along the way. The message is, "You are not alone, we are here to help you; we will practice together until you are comfortable giving yourself an injection." **A3**
- With all patients, it is important to explain that insulin is not a punishment or a failure. Insulin is the best treatment we have for managing blood glucose levels. For patients with type 1 diabetes it is the primary treatment, and for patients with type 2 diabetes it is often an adjunct to oral therapy to improve blood glucose control. For patients with type 2 diabetes it is important that they understand the natural progression of the disease and that insulin therapy is a part of the logical progression in its management (Paul Hofman, MD, oral communication, October 24, 2015).[146,147,224-226] **A3**
- Patients should understand that improving blood glucose control will make them feel better. Many patients report an overall improvement in their health and well-being when taking insulin. The message is, "You will not be urinating as frequently and should sleep better. You will have more energy and improved vision. Managing blood glucose with insulin will also help prevent long-term complications."[147,227] **A3**
- Patients, especially adolescents, should be given as much control as possible in designing their regimen to fit their lifestyle. This could include basal bolus therapy, carbohydrate counting, and using insulin pens and insulin pumps. **A3**

Strategies for Reducing Fear, Pain, and Anxiety.

- Include caregivers and family members in the planning and education of the patient, and tailor the therapeutic regimen to the individual needs of the patient. **A3**
- Have a compassionate and straightforward approach when teaching injection technique. Demonstrate the injection technique to the patient. Have the patient follow along and then demonstrate correct technique back to the educator or HCP. **A3**

- Consider using devices that hide the needle in case of anxiety provoked by seeing sharps. Also consider using vibration, cold temperature, or pressure to "distract" the nerves (gate control theory) from the perception of pain. **A3**
- Children have a lower threshold for pain. The HCP should ask about pain (Paul Hofman, MD, oral communication, October 24, 2015).[224] For young children, consider distraction techniques or play therapy (such as injecting a soft toy [stuffed animal or doll]). Older children often respond better to cognitive behavioral therapies,[226] such as guided imagery, relaxation training, active behavioral rehearsal, graded exposure, modeling, positive reinforcement, and incentive scheduling. **A2**
- Fear and anxiety may be substantially reduced by having the parent and child give themselves a dry injection. Often they are surprised and relieved at how painless the injection is. **A2**
- Use of injection ports at the commencement of therapy may help reduce anxiety and fear of injections and its associated pain.[227-230] **B1**
- Insulin pens with very short needles may be more acceptable to patients than the syringe and vial. This should be discussed with the patient and family when teaching injection therapy. The 4-mm pen needle is reported by patients to be less painful than longer needles.[96,104,148,227] **A2**
- Patients who occasionally experience sharp pain on injection should be reassured that the needle may have touched a nerve ending, which happens randomly and will not cause any damage. If pain persists the HCP should see the patient and evaluate the injection technique. **A3**
- Keep insulin at room temperature for a more comfortable injection. Injecting insulin while it is still cold often produces more pain. **A3**
- If bleeding or bruising occur, reassure the patient that these do not affect the absorption of insulin or overall diabetes control. If bruising continues or hematomas develop, observe the injection technique and suggest improvements (eg, better rotation of injection sites). **A3**

Tips for Injection Education.

- Demonstrate proper injection technique to the patient and family. Then have the patient and family demonstrate proper technique back to the HCP. **A3**
- Ensure that the skin is clean and dry before injecting. Patients usually do not need to use a disinfectant on the skin, but if they do, they should allow it to dry completely before injecting. **A3**
- Use needles of shorter length (4 mm or the shortest available) and smaller diameter (highest gauge number), and the tip with the lowest penetration force to minimize pain. Use a sterile, new needle with each injection. **A1**
- Insert the needle through the skin in a smooth but not jabbing movement. Pain fibers are in the skin, and going through the skin too slowly or too forcefully may increase the pain. **A1**
- Inject the insulin slowly, ensuring that the plunger (on the syringe) or thumb button (on the pen) has been fully depressed and all the insulin has been injected. With pens, the patient should count to 10 after the button has been depressed before withdrawing the needle to get the complete dose. **A3**
- The HCP should teach the importance of rotation and create a rotation pattern with the patient when initiating injection therapy. The message should be: "Insulin will not be well-absorbed if it is always injected into the same area. It is important to move injections at least half an inch (1 cm) away from the previous injection and to use all injection sites on the body (back of the arms, buttocks, thighs, and abdomen)." **A1**
- If the same injection site is used repeatedly it may become lumpy, firm, and enlarged. The insulin will not work correctly if injected into these areas. **A1**
- If pain is experienced when injecting large volumes of insulin the dose may need to be divided into 2 injections of smaller volume or the concentration of insulin may need to be increased. **A3**

TECHNOLOGY

1 Person/1 Pen

Sometimes macroscopic blood regurgitation into a cartridge is observed. Should the

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cartridges be used by another patient, this could result in the transmission of bloodborne diseases such as human immunodeficiency virus or hepatitis. More concerning is microscopic blood because the risk exists but there is no visible clue. Even one injection with an insulin pen can contaminate the insulin cartridge with biologic, possibly infectious, material. If the same cartridge is used to inject another patient, transmission of this material could occur, even if a new needle is used. The implication is clear: there should never be sharing of insulin pen cartridges between patients. Additional studies on this risk are summarized in Supplemental Appendix 12 (available online at http://www.mayoclinicproceedings.org).[231-234]

Recommendations.

- Insulin pens, pen cartridges, and small individual vials should not be shared to prevent the transmission of infectious diseases. One patient/1 insulin pen. **A1**
- Insulin pens, pen cartridges, and small individual vials should be clearly labeled with patient names/identifiers in health care facilities where common storage is used, eg, refrigerators. **A2**

Insulin Infusion Sets for CSII

Continuous SC insulin infusion using an insulin pump has been a treatment modality for patients with diabetes, primarily those with type 1, for more than 30 years.[235] Insulin infusion sets (IISs) are required to deliver insulin into the SC tissue, but their role in CSII therapy is often underappreciated by HCPs. As a result, advances in IIS technology are stagnant and overshadowed by the innovative advances of insulin infusion pumps. There are, nevertheless, a large variety of IIS options available. Complications related to IISs are common and include infusion site, technical, and metabolic manifestations; for these reasons, IISs are considered the Achilles heel of CSII.[236]

In a randomized, open-label, pharmacokinetic study by McVey et al,[237] irregularities in insulin delivery during CSII were observed when in-line pressure was used as an indicator for flow. Significant increases in pressure during infusion (which suggests flow interruptions) were found over a 24-hour period in 20 adults with type 1 diabetes, often without triggering the pump's occlusion alarm. The authors concluded that these silent, or subalarm, occlusions may potentially contribute to unexplained hyperglycemia in patients receiving CSII.

Hirsch[238] reported the occurrence of silent occlusions using insulin diluent in healthy volunteers, in whom pressure measurements were made. Silent occlusion was defined as a continuous rise in pressure of at least 30 minutes without triggering the pump occlusion alarm. These pressure-rise events occur frequently during SC infusion (>35% of infusions). Furthermore, these studies evaluated the efficacy of a catheter with an additional lumen on its side (known as a side-ported catheter) for reducing flow interruptions or silent occlusions. The use of a side-ported set lowered the incidence of silent occlusions by more than 75% compared with a conventional Teflon IIS.[239]

Similar criteria for choosing needle length for pen needles should apply to choosing optimal IIS cannula length. Skin thickness studies suggest that short cannula lengths are appropriate to help reduce the risk of IM insertion. Bolick[240] conducted corollary imaging studies using both fluoroscopy (in swine) and magnetic resonance imaging (in human volunteers) to characterize the IIS performance during infusion and bolusing. The studies provide visual evidence that IIS cannulas measuring 9 mm or longer may increase the risk of IM insertion, particularly in body areas of reduced adipose tissue, such as the back of the arm and the thigh. A summary of other studies on the delivery issues surrounding CSII is presented in Supplemental Appendix 13 (available online at http://www.mayoclinicproceedings.org).[161,241-244]

Recommendations.

- Population studies suggest that CSII cannulas should be changed every 48 to 72 hours with the goal of minimizing infusion site adverse events and potential metabolic deterioration. However, these times are patient dependent and should be adjusted accordingly. **A1**
- All CSII users should be taught to rotate infusion sites along the same principles

that injecting patients are taught to rotate injection sites. **A1**

- All CSII patients with unexplained glucose variability, including frequent hypoglycemia/hyperglycemia, should have infusion sites checked for LH, nodules, scarring, inflammation, or other skin and SC conditions that could affect insulin flow or absorption. **A1**
- All CSII patients should have their infusion sites checked regularly (at least annually) for LH by an HCP. **A1**
- If LH is suspected, the patient should be instructed to stop infusing into these lesions and to insert the catheter into healthy tissue. **A1**
- Silent occlusion or interruption of insulin flow should be suspected in any person with unexplained glucose variability, unexplained hyperglycemia, or frequent hypoglycemia/hyperglycemia. **B2**
- If silent occlusion is suspected, CSII patients should be considered for an alternative catheter. **A1**
- All CSII patients should be considered for the shortest needle/cannula available, along the same principles as insulin injectors, to minimize the risk of IM infusion. Young children and very thin individuals may need to insert into a lifted skinfold to avoid IM insertion. **B2**
- The smallest-diameter needle/cannula should be considered in CSII patients to reduce pain and the occurrence of insertion failure. **B2**
- Angled IISs should be considered in CSII patients who experience infusion site complications with 90° IISs. **B2**
- All CSII patients who experience a hypersensitivity reaction to cannula material or adhesive should be considered for alternative options (alternative sets, tapes, or skin barriers). **A3**
- CSII patients who are lean, muscular, or active and have a high probability of the cannula or tubing being dislodged may benefit from angled (30°-45°) insertion of their IIS.[245] **C3**
- CSII patients who have difficulty inserting their IIS manually for any reason should insert it with the assistance of a mechanical insertion device. **C3**
- CSII patients who become pregnant may require adjustments to their IISs, infusion site locations, and frequency of site changes. **B3**

Needlestick Injuries/Bloodborne Infection Risk

Needles for delivering insulin are the most commonly used sharps in the world. When combined with lancet use for drawing blood, the use of medical sharps by persons with diabetes is far greater than that by any other patient population. Most sharps use is in the home setting by persons whose serostatus for hepatitis, human immunodeficiency virus, and other bloodborne pathogens is unknown. Thus, needlestick injuries (NSIs) from diabetes sharps are an important public health issue. Technologies have emerged in recent years to address the potential infection risk in this population, but they are not widely known or used. A full summary of the literature regarding NSI risk when delivering insulin is presented in Supplemental Appendix 14 (available online at http://www.mayoclinicproceedings.org).[246-272]

Recommendations.

- Safety-engineered devices play a critical role in protecting injectors, pump users, and downstream workers. Nurses and other HCPs at risk must receive appropriate education and training in how to minimize risk by following optimal techniques, using safety devices, and wearing appropriate protective clothing (eg, gloves). **A1**
- Safety injection devices should be considered first-line choice if injections are given by a third party. Pens and syringes with needles used in this setting should have protective mechanisms for all sharp ends of the delivery device. **A2**
- The HCPs should be involved in the trialing and choice of devices to be used in their health care setting. Evaluation before adoption should include key specialists (eg, infection control, occupational health, and experienced end users).[273,274] **A1**
- Health care settings where insulin pens are used must follow a strict 1 patient/1 pen policy. **A2**

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- Manufacturers should investigate all reported NSIs to determine whether they are related to a device failure. **A3**
- To minimize the risk of NSI through a skinfold, the use of 4- and 5-mm pen needles or 6-mm insulin syringe needles without a skinfold is recommended. If a lifted skinfold is used, the patient should ensure that the finger and thumb are approximately 1 inch (25 mm) apart and should make the injection in the center of the fold, thus minimizing through-skinfold NSI risk. **A2**
- Campaigns to increase NSI awareness should be conducted regularly and should involve all persons at potential risk for NSI. **A1**
- Needle recapping should not be done, and HCPs should be especially trained to avoid needle recapping. Manufacturers should develop devices that automatically and passively prevent needle recapping. **A2**
- Hospitals should encourage reporting of NSIs and near misses and should establish a blame-free culture. Review of all NSIs and near misses should take place regularly to assess educational needs and allow for policy change. **A1**
- A review of adherence to guidelines and appraisal of the effectiveness of education and training should be performed at regular intervals. A reporting system for violations should exist. **A2**
- Proper use of safety devices is essential to their effectiveness. When they are not activated, because of user forgetfulness, lack of training, or inattention, they afford no additional risk reduction over nonsafety (conventional) devices. **A1**
- Sharps containers should be easily accessible at the point of care or beside the patient before the injection or infusion. Containers should bear the following or a similar warning: "Needles may seriously damage the health of others. Please ensure their safe disposal." **A2**
- Although hepatitis B virus vaccination should be universal, at minimum it should be offered by the employer to all workers exposed to sharps. Vaccination status must be reviewed every year at the employee's performance assessment.[275] **A1**
- First aid information about what to do in the event of an NSI should be readily available in all health care facilities. **A2**
- All workers in possible contact with sharps should know the local safety and disposal regulations. The societal and legal consequences of not adhering should be reviewed.[276] **A2**
- Safe disposal of sharps should be taught to patients and caregivers from the beginning of injection or infusion therapy and reinforced throughout.[277] **A2**
- Potential adverse events of NSIs should be emphasized to the patient's family, caregivers, and service providers (eg, housekeepers and trash collectors). **A3**
- Used sharps should never be discarded into the public trash. **A3**

DISCUSSION

In 2010, after the 2009 Third Injection Technique Workshop in Athens (TITAN), a comprehensive set of injection recommendations was published.[1] This document provided the stimulus to many country-specific initiatives. The Forum for Injection Technique (FIT), a community of experienced diabetes specialist nurses dedicated to best practice in injection technique, began in the United Kingdom shortly after TITAN and spawned many other FIT groups throughout the world. As of 2016, there are FIT boards in the United Kingdom, Ireland, Canada, Dominican Republic, South Africa, Korea, Norway, the Philippines, Taiwan, Switzerland, and India.[278,279]

Similar initiatives in other countries (eg, Turkey, Belgium, Italy, Germany, and China) do not carry the FIT name but have led to similar guidelines.[280-285] These country initiatives play a critical role in establishing best practice and in changing behavior for countless patients and HCPs worldwide. Such guidelines should be updated regularly. Some countries (eg, Canada and the United Kingdom) now publish their guidelines only online to have more flexibility when updating, increase ease of access, and save on resources.

In these new recommendations we added a variety of themes (eg, infusion, safety) and covered all the key studies published since TITAN. However, a variety of key injecting parameters have not been studied in sufficient depth and in specific populations

for recommendations to be made. These parameters include injections during pregnancy, injections using the newer analogues or GLP-1 receptor agonists, and injections in special populations (eg, babies and the very elderly) or under special conditions (eg, SC edema). Investigators are encouraged to address these issues through prospective, randomized clinical trials.

CONCLUSION

These evidence-based recommendations provide a new, practical, and comprehensive set of guidelines for patients and professionals worldwide. If followed, they should ensure safe and efficacious delivery of diabetic therapies into the SC space. To assist with implementation of these new recommendations, we provide 6 sets of golden rules in the Appendix. These rules are meant as a clear and simple road map for nurses, educators, and patients. If the rules are followed, nearly all of the new recommendations will be implemented.

APPENDIX. SIX SETS OF GOLDEN RULES TO ASSIST WITH IMPLEMENTATION OF THE NEW RECOMMENDATIONS

Injection Technique in Adults

1. Insulin and glucagon-like peptide-1 receptor agonists must be deposited into healthy subcutaneous fat tissue, avoiding the intradermal and IM spaces as well as scars and LH.
2. 4-mm pen needles inserted at 90° are recommended for all adults regardless of age, sex, ethnicity, or BMI. If patients need to use needle lengths >4 mm or a syringe (or where the presumed skin surface to muscle distance is less than the needle length), they must use a correctly lifted skinfold to avoid IM injections.
3. Recommended sites for injection are the abdomen, thigh, buttock, and upper arm:
    a. Abdomen within the following boundaries: ~1 cm above the symphysis pubis, ~1 cm below the lowest rib, ~1 cm away from the umbilicus, and laterally at the flanks
    b. Upper third anterior lateral aspect of both thighs
    c. Posterior lateral aspect of both upper buttocks and flanks
    d. Middle third posterior aspect of the upper arm
4. Detect and avoid injection into areas of lipodystrophy.
5. Rotation of injection sites is critically important and can be correctly performed by:
    a. Spacing injections within a site approximately 1 fingerbreadth apart
    b. Using a single injection site no more frequently than every 4 wk.

Injection Technique in Children

1. Insulin must be deposited into healthy subcutaneous fat tissue, avoiding the intradermal and IM spaces as well as scars and LH.
2. Injection should avoid bony prominences by 1 to 2 adult fingerbreadths. Preferred sites are:
    a. Abdomen, 2 adult fingerbreadths away from the umbilicus
    b. Upper third anterior lateral aspect of both thighs
    c. Posterior lateral aspect of both upper buttocks and flanks
    d. Middle third posterior aspect of the upper arm
3. Consideration should be given to the type of insulin and the time of day when selecting injection sites.
4. Correct rotation of injection sites must be followed at all times to prevent LH. 4-mm pen needles should be used for all children and young adults regardless of age, sex, ethnicity, or BMI.
5. Children and young adults are at risk for accidental IM injection. A 2-finger lifted skinfold usually prevents IM injection but is much less effective in the thigh than in the abdomen. Lean children should use a lifted skinfold when the presumed skin surface to muscle distance is less than the needle length plus 3 mm.

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Treating and Preventing LH

1. All patients who inject or infuse insulin must have their sites checked at every regular visit, or at least every year:
    a. HCPs in diabetes must be trained to correctly screen for LH and other site complications.
    b. All persons who self-inject/infuse insulin or other injectables must be taught to self-inspect sites and be able to distinguish healthy from unhealthy tissue.
2. Clinicians must monitor and record the evolution of LH, possibly using photography (with the patient's consent); body maps with descriptors for size, shape, and texture; or transparent graduated recording sheets.
3. With patient consent, clinicians should mark the border of all LH and other site complications with skin-safe single-use markers and instruct patients to avoid using marked areas until instructed otherwise.
4. Patients with LH who have been instructed to stop injecting/infusing into affected tissue must be:
    a. Allowed to experience the actual metabolic difference it makes to use normal tissue instead of LH (this is a key to long-term adherence)
    b. Informed that some mild pain may be experienced when injecting into normal tissue
    c. Supported by an HCP to monitor glucose levels frequently due to the risk of unexpected hypoglycemia
    d. Assisted in the reduction of their insulin doses in line with glucose results, knowing that reductions often exceed 20% of their original dose
    e. Optimized to 4-mm pen needles/6-mm insulin syringes or the shortest needle length available to minimize accidental IM risk due to using larger zones
    f. Optimized to advanced needle geometry, including thin-walled and extra-thin-walled needles (if available) to minimize pain and discomfort and to maximize ease of dosing when injecting into healthy tissue
5. All patients must be supported to correctly rotate injection/infusion sites and cautioned about the risks of reusing needles to minimize risk of injection site complications.
    a. Principles of correct rotation technique must be taught to patients, and rotation technique must be assessed at least every year and more frequently if required.
    b. Correct rotation ensures that injections are spaced out approximately 1 cm (a fingerbreadth) from each other and that a single injection site is used no more frequently than every 4 wk.

Psychological Issues Regarding Insulin Delivery

1. All patients and caregivers should be offered general and individualized education/counseling that will facilitate optimal care.
2. Ensure that all patients and caregivers are supported by their HCP using patient-centered evidence-based psychological educational tools and strategies to achieve mutually agreed goals.
3. Diabetes care HCPs should be skilled in identifying psychological issues that impact insulin delivery.
4. HCPs must have a range of therapeutic behavioral skills to minimize the psychological distress and the impact of insulin therapy.
5. Various methods of minimizing pain and fear of injection should be used to reduce the psychological impact.

Needlestick Injuries and Sharps Disposal

1. All HCPs, employers, and employees must comply with relevant international, national, and local legislation for the use of sharps.
2. Sharp medical devices present a potential risk of injury and transmission of disease. All HCPs, employers, and employees must ensure the safest possible working environment by:
    a. Conducting regular risk assessment and providing continuing education and training
    b. Providing and using a means of safe disposal of used sharps
    c. Prohibiting needle recapping
    d. Encouraging reporting of incidents

3. Safety engineered devices must be used by all HCPs and by all third-party caregivers using sharps (eg, injections, blood testing, infusion) in all hospitals, clinics, and other institutions, such as schools and prisons. Best practice for pen needles requires that both ends of the needle be protected.
4. Safe disposal requires that:

    a. Correct disposal procedures and personal responsibility be taught to patients and caregivers by the dispensing clinician (including pharmacists) and be regularly reinforced
    b. Safe sharps disposal systems and processes be present and known to all persons at risk for sharps contact
    c. Environments where others are at risk (eg, care homes, schools, and prisons or around rubbish workers and cleaners) be provided safety education and safety devices
    d. Patients diagnosed as having bloodborne diseases such as human immunodeficiency virus and hepatitis be supported to use safety-engineered devices and dispose of them safely
    e. Sharps never be placed directly in public or household trash

Insulin Infusion

1. Insulin infusion cannula must be inserted into healthy subcutaneous fat tissue, avoiding underlying muscle as well as areas of skin irritation, scarring, LH, and lipoatrophy.
2. If bleeding or significant pain occurs on insertion, the set should be removed and replaced.
3. Preferred sites for infusion cannula should be individualized but include:

    a. Abdomen, avoiding bony prominences and the umbilicus
    b. Upper third anterior lateral aspect of both thighs
    c. Posterior lateral aspect of both upper buttocks and flanks
    d. Middle third posterior aspect of upper arm

4. Infusion cannula sites should be rotated to avoid complications. This usually involves moving to a new location. In-site duration should be individualized but typically should not be more than 72 hours.
5. If kinking occurs, consider a shorter cannula or an oblique or steel set. If frequent silent occlusions or unexplained hyperglycemia occur, consider using a different type of infusion set, including a cannula with a side port, if available.

BMI = body mass index; HCP = health care professional; IM = intramuscular; LH = lipohypertrophy.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **CSII** = continuous subcutaneous insulin infusion; **FIT** = Forum for Injection Technique; **FITTER** = Forum for Injection Technique and Therapy: Expert Recommendations; **GLP-1** = glucagon-like peptide-1; **HCP** = health care professional; **IM** = intramuscular; **ITQ** = Injection Technique Questionnaire; **LH** = lipohypertrophy; **NPH** = neutral protamine Hagedorn (also known as Insulin N); **NSI** = needlestick injury; **SC** = subcutaneous; **TITAN** = Third Injection Technique workshop in AtheNs

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